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| 09/867,924 | 05/30/2001 | Blake J. Roessler | UM-06191 | 7554 |

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| EXAMINER | |
|---|---|
| FUBARA, BLESSING M | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/867,924 | ROESSLER ET AL. | |
| | Examiner | Art Unit | |
| | BLESSING M. FUBARA | 1618 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *25,26,28-42,45-55 and 65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25, 26, 28-42, 45-55 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The examiner acknowledges receipt of request for continued examination under 37 CFR 1.114, request for extension of time, amendment and remarks filed 3/24/08. Claim 25 is amended. Claims 25, 26, 28-42, 45-55 and 65 are pending.

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/24/08 has been entered.

### *Response to Arguments*

**Previous rejections that are not reiterated herein are withdrawn.**

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 25, 26, 28-42 and 45-54 and 65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is new matter rejections.

4. Skin patch membrane recited in claim 25 is not envisioned by the as filed specification. This rejection may be overcome by removing the new matter from the claims.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 25, 26, 28-42 and 45-54 and 65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 recite a method and steps of providing a composition and contacting the composition with a tissue without saying what the method is doing. It thus appears that the claim is incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: what the method is.

However, the claims are examined as a method for delivering biological agent to a tissue by method steps a and b.

***Claim Rejections - 35 USC § 102***

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 55 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Szoka, Jr. et al. (US 5,661,025) or Tomalia et al. (US 5,714,166).

Szoka describes a self-assembling polycation delivery system that comprises a dendrimer polycation and polynucleotide and optionally two or more of DNA masking agents, Cell recognition agents, charge-neutralization and membrane-permeabilizations agents and subcellular localization agents (abstract; column 4, line 63 to column 5, line 13) with the nucleic acid of the claim reading on the polynucleotide of the prior art; and when the polynucleotide is RNA or DNA, the composition of Szoka anticipates the generic claim to composition containing dendrimer and nucleic acid as in claim 55. The composition is anticipated for transdermal administration (column 19, lines 18, 34-36, 56) such that the transdermal administration meets the limitation of a skin patch.

Tomalia describes DNA-dendrimer (starburst polymer) conjugates (column 1, lines 46-65; column 2, lines 12-30, 56, 57; column 4, line 56 to column 11, line 32; column 54, lines 7-18), the composition is transdermally delivered (column 54, lines 14 and 15) to target areas. The transdermal administration meets the limitation of a skin patch.

While both Tomalia (column 49, line 44; column 50, lines 12, 47; column 52, line 1; claim 124) and Szoka (column 2, line 33; columns 3 and 4; column 20, lines 28-34) talk about transfecting cells, it is noted that the recitation of transfecting a tissue is the intended use of the composition.

In the alternative, neither Tomalia nor Szoka use the term skin patch. But transdermal delivery is known to involve the use of skin patch as evidenced by Dondio et al. (US 5,922,887)

at lines 59 and 60 and by Loike et al. (US 5,855,881) at column 33, lines 44-49) so that taking the general teachings of either Szoka or Tomalia, one of ordinary skill in the art would be using skin patch in the transdermal application. Desiccation prevents or controls the amount of moisture that may be contained with the transdermal delivery system as evidence by paragraphs [0012] and [0059] and [0087] of US 20050214354.

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 25, 26, 28-42, 45-55 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foldvari et al. ("Cutaneous vaccination: the skin as an immunologically active tissue and the challenge of antigen delivery," in Journal of Controlled Release, Volume 66, Issues 2-3, 15 May 2000, Pages 199-214) and Baker et al. ("Regulation of in vivo gene expression using antisense oligonucleotides or antisense expression plasmids transfected using starburst PAMAM dendrimers," in Nucleic Acids Research, 1996, Vol. 24, No. 11, pp 2176-2182) in view of Park et al. (US 6,267,987).

11. Foldvari discloses transdermal delivery of protein or nucleotide to the skin tissue (pp. 71-86). Foldvari discloses on page 205 that dendrimers are known to deliver DNA. Foldvari discloses cutaneous vaccination (title). The skin (paragraph 2) through which the vaccine is

administered meets the limitation of skin tissue cells of the claims. Foldvari discloses dendrimers that are complexed with DNA in spherical structures and the dendrimers and the DNA can be delivered to cell lines (right column, first full paragraph of page 205). Acrylate, PAMAM and polyethyleneimine polymers are some of the polymers listed that are used with the DNA (right column, page 205). Furthermore, Foldvari discloses the use of PLGA, PLA, lactides and glycolides for delivery of protein, carbohydrate or DNA vaccines (right column, page 204). These polymers are biocompatible and biodegradable. Liposomes are also used to deliver beneficial agents (paragraph 3.4). DNA oligonucleotide meets nucleic acid of the claims.

Regarding claim 26, Baker describes transfer of oligonucleotides in cell culture (abstract). Baker discloses the use of PAMAM dendrimers for effective delivery of oligonucleotides evaluated in vitro cell culture system (abstract, right column of page 2177). Park discloses polyester based dendrimer system for delivery of oligonucleotides (abstract; column 2, lines 3-5, 36-40; column 3, lines 24-34; column 4, lines 1-46; column 9, lines 8-17). Baker discloses the use of dendrimers to deliver DNA (pp 2176-2182).

Regarding biocompatible membrane of claim 32, 33 and 35, Foldvari describes microencapsulation in polyester membranes (microspheres, liposomes) and the polyesters are bioerodible. Regarding the collagen of claim 36, it would be obvious to substitute one membrane material for another and still expect effective delivery of the nucleotides. For example, collagen is an essential protein, which can be found in skin, connective tissue, blood vessels, bone and other parts of the body and collagen and PLGA have been used as membrane materials with dendrimer to deliver DNA (see abstract of Bielinska et al. “Application of

membrane-based dendrimer/DNA complexes for solid phase transfection in vitro and in vivo" in Biomaterials, Vol.21, Issue 9, May 2000, pages 877-997, as a teaching reference).

The DNA meets the requirement of claims 25 and 45 as biological agent that is nucleic acid..

Wound healing, encoding growth factor are all functions of DNA; protein that comprises protein that promotes tissue vascularization is the function of the protein. Thus claims 46, 47, 48, 49, 51, 52, 53 and 54 are met.

Therefore, the motivation to combine the references flows from teaching in the references that oligonucleotides are deliverable by dendrimers that are composed of polyesters (Foldvari and Park) and expected to successfully deliver the nucleotides to the tissues that are contacted with the dendrimer (abstract of Baker). Therefore, the cited references provide methods where the tissue and dendrimer compositions are brought into contact for the delivery of oligonucleotide. Regarding "active concentrations" in the phrase "contacting said tissue with said composition such that said biological agent is provided to said tissue at biologically active concentrations," it is noted that active concentration reads on any amount and since the prior art delivers oligonucleotide to tissues or cells, the prior art would meet any amount within the broad active concentrations claimed.

The combination of Foldvari and Baker discloses the use of dendrimers for the delivery of proteins or DNA. The combined reference failed to disclose the presence of polyester for the delivery. But Park discloses polyesters as carriers for delivery of nucleic acids (abstract). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the combined teaching of Foldvari and Baker for the delivery of DNA or

protein. One having ordinary skill in the art would have been motivated to incorporate polyesters with dendrimer and expect to successfully deliver DNA.

***Response to Arguments***

12. Applicant's arguments filed 3/24/08 have been fully considered but they are not persuasive.

a) Applicant argues that none of the cited references in combination or alone teaches skin patch membrane that is associated with at least one dendrimer and at least one biological agent comprising nucleic acid. The examiner disagrees because Foldvari teaches transdermal delivery of protein of nucleotide to skin tissue (pp. 71-86) as described above. The dendrimer is associated with the nucleotide, which is a biological agent. Transdermal delivery is known to involve the use of skin patch as evidenced by Dondio et al. (US 5,922,887) at lines 59 and 60 and by Loike et al. (US 5,855,881) at column 33, lines 44-49). It is also noted that it is noted that Park discloses polyesters based dendrimers for delivery of oligonucleotides/nucleic acids (abstract) according to the description in the rejections above; Baker discloses the use of PAMAM dendrimers for the effective delivery of oligonucleotide/nucleic acids according to the description in the rejections above; Foldvari teaches transdermal delivery of DNA/nucleic acids/oligonucleotides (paragraph 4 of page 205). Transdermal delivery generally involves the use of a skin patch or membrane on the skin for the delivery of actives through the dermis into the blood stream and because the skin tissue has skin tissue cells, transdermal delivery involves the participation of skin tissue cells as evidenced by Banga et al. in vol. 16, issue 10, pp. 408-412

of the Trends in Biotechnology and by pages 1596 and 1597 of the 18th edition of Remington's Pharmaceutical Sciences, edited by Gennaro, 1990.

b) Applicant also argues that Foldvari does not teach the use of skin-patch membrane; that is associated with at least one dendrimer and at least one biological agent comprising nucleic acid but that Foldvari teaches specific forms of transdermal delivery devices that do not include skin-patch membrane as required by the instant claims. While Foldvari does not specifically teach skin patch, it is noted that the rejection is made under 35 USC 103 and it is also known that transdermal delivery is known to involve the use of skin patch as evidenced by Dondio et al. (US 5922,887) at lines 59 and 60 and by Loike et al. (US 5,855,881) at column 33, lines 44-49).

c) Applicant also argues that Banga and the Remington reference do not overcome the deficiencies of the Foldvari Banga deals with electroporation and the Remington reference does not describe transdermal delivery of nucleic acid. But Banga and Remington are cited as evidence references that show that transdermal delivery involves the use of skin patches or membranes.

d) Applicant argues that the cited prior art does not teach transfection as described in Examples 9-13. But Examples 10-13 describes determination of delivered biological agent from the skin tissues, Example 9 describes harvesting the skin for transfection assays. Thus, the examiner disagrees. Claim 25 contacts skin tissue with the composition from step a (ii) to effect transfection, and in the same way, the prior art contacts skin tissue with composition that comprises dendrimer associated with nucleotide. Since the contacting of the composition with skin tissue cells leads to transfection and since transfection is the introduction of DNA into tissue

cells, the prior art that contacts skin tissue with DNA containing dendrimer would also lead to transfection of the DNA onto the skin tissue.

e) Applicant argues that one skilled in the art would not be motivated to modify the transdermal delivery devices of Foldvari into skin patch delivery system. The examiner disagrees. The art recognizes transdermal delivery to involve the use of skin patch as evidenced by Dondio et al. (US 5922,887) at lines 59 and 60 and by Loike et al. (US 5,855,881) at column 33, lines 44-49). that prior to the instant Examples 1-13, it was not known that skin patch membranes could effectively transfect nucleic acid associated with dendrimers so that one skilled in the art would not obtain sufficient guidance from the cited and that the examiner failed to provide the motivation to modify the transdermal delivery device of Foldvari to the skin patch membrane of the invention.

Therefore, the cited references in combination teach transdermal delivery system comprising DNA associated with dendrimer where the DNA is at least one biological agent and the method of the claims is met when the transdermal delivery device containing the DNA-dendrimer is brought into contact with the skin tissue. The prior art is what is known in the prior art. The prior art teaches the ability to transdermally deliver nucleic acid before applicant's invention according to the teaching of Foldvari. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Applicant has not provided a showing that the nucleic acid cannot be delivered transdermally as taught by Foldvari, keeping in mind that transdermal delivery is topical and via skin tissue cells. It is known in the prior art that transdermal delivery utilizes

patch that is topically affixed to the skin as evidenced by Banga et al. and the 18th edition of Remington's Pharmaceutical Sciences (see second full paragraph, page 6 above).

13. Claims 25, 26, 28, 40, 41, 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Szoka, Jr. et al. (US 5,661,025) or Tomalia et al. (US 5,714,166).

14. To expedite the prosecution, the claims are examined as method for delivering biological agent by steps a and b and the contacting of the tissue with the composition leads to transfection.

Szoka describes a self-assembling polycation delivery system that comprises a dendrimer polycation and polynucleotide and optionally two or more of DNA masking agents, Cell recognition agents, charge-neutralization and membrane-permeabilizations agents and subcellular localization agents (abstract; column 4, line 63 to column 5, line 13) with the nucleic acid of the claim reading on the polynucleotide of the prior art; and when the polynucleotide is RNA or DNA, the composition of Szoka anticipates the generic claim to composition containing dendrimer and nucleic acid as in claim 55. The composition is anticipated for transdermal administration (column 19, lines 18, 34-36, 56) such that the transdermal administration meets the limitation of a skin patch.

Tomalia describes DNA-dendrimer (starburst polymer) conjugates (column 1, lines 46-65; column 2, lines 12-30, 56, 57; column 4, line 56 to column 11, line 32; column 54, lines 7-18), the composition is transdermally delivered (column 54, lines 14 and 15) to target areas. The transdermal administration meets the limitation of a skin patch.

While both Tomalia (column 49, line 44; column 50, lines 12, 47; column 52, line 1; claim 124) and Szoka (column 2, line 33; columns 3 and 4; column 20, lines 28-34) talk about

transfecting cells, it is noted that the recitation of transfecting a tissue results from contacting the tissue with composition comprising DNA and dendrimer. But transdermal delivery is known to involve the use of skin patch as evidenced by Dondio et al. (US 5922,887) at lines 59 and 60 and by Loike et al. (US 5,855,881) at column 33, lines 44-49) so that taking the general teachings of either Szoka or Tomalia, one of ordinary skill in the art would be using skin patch in the transdermal application.

***Double Patenting***

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 55 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 7 of copending Application No. 11/503,742. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 4 and 7 teaching a composition comprising a dendrimer and nucleic acid meets the limitations of composition claim 55 of the examined claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claim 55 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5, 6 of U.S. Patent No. 7,078,461. Although the conflicting claims are not identical, they are not patentably distinct from each other because the composition in issued claims 1-3, 5 and 6 meets the limitations of examined composition claim 55.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BLESSING M. FUBARA whose telephone number is (571)272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Blessing M. Fubara/

Examiner, Art Unit 1618